



## INSIDE THIS ISSUE:

New Drug Update	<u>1</u>
Drug Information Corner	<u>2</u>
Literature Review	<u>3</u>
Clinical Specialist Corner	<u>4</u>
Formulary Changes	<u>4</u>
Patient Safety Alerts	<u>5</u>
New Drug Update (Cont.)	<u>6</u>
Name that Drug	<u>6</u>

## Letter From The Editors

It is an exciting time of the year as the weather is finally beginning to improve and summer is fast approaching. College students are finishing up finals, and kids are beginning to dream of summer vacation, much to the horror of parents everywhere. Naturally this means another edition of the Pharmacotherapy Newsletter to top your summer reading lists.

In this edition of the newsletter we review the treatment of pulmonary hypertension in the New Drug Update section, looking at the novel therapy riociguat. Then Samantha Schott, a PharmD candidate from Wilkes University, explores the potential link between antibiotics and dysglycemias; and, Christina Inteso, another PharmD candidate from Wilkes and future PGY-I resident at the Lebanon VA, delves into the literature sup-

porting bromocriptine's approval for the treatment of type II diabetes.

Old favorites like the Clinical Specialist Corner are also covered in this edition of the newsletter as well as the latest patient safety alerts from the FDA and changes to the VA National Formulary. The newsletter finishes up with some fun, challenging you to guess the medication names by sounding out the picture clues. (Hint: those with Lionshead experience will be particularly familiar with this activity.)



Finally, as this will be the last edition of the newsletter prior to the annual changing of the residents, I would also like to take this opportunity to thank the entire pharmacy staff on behalf of the 2013-2014 pharmacy residents for making this a wonderful year.

Thanks again and enjoy your summer!

Andy Santeusano, PharmD  
Dina Hunsinger-Norris, PharmD,  
BCPS, AQ-Cardiology

## New Drug Update: Adempas<sup>®</sup> (riociguat) for Pulmonary Hypertension

Pulmonary hypertension, characterized by elevated pulmonary arterial pressure and secondary right ventricular failure, is a progressive disease that if left untreated is associated with a high rate of mortality. Patients with pulmonary hypertension can be classified into 1 of 5 groups based on etiology of

the disease. Group 1 is idiopathic in nature, group 2 is caused by left-sided heart disease, group 3 is associated with pulmonary disease, group 4 is due to thromboembolic causes, and group 5 is multifactorial in nature. Treatment of these patients typically consists of management of the underlying factors causing the

disease as well as vasodilators in order to reduce cardiac pressures and increase perfusion. Riociguat is a novel therapy found to stimulate soluble guanylate cyclase and the receptor for nitric oxide resulting in arterial dilation, increased blood flow, and decreased pulmonary pressure. (Continued on [Page 6](#))



# Drug Information Corner

## Fluoroquinolones: Scapegoat or Diabetic Enemy?

By: Samantha Schott, PharmD. Candidate 2014



*“Close attention should be paid to glucose levels whenever high risk patients are ill, as the body’s adrenergic response to infection and changes in the patient’s behavior while ill will both affect glucose metabolism.”*

The question of antibiotics’ effects on blood glucose seems to arise often. Clinicians and patients alike may be prone to point the finger at a newly prescribed antibiotic when glucose levels change abruptly, but the association is not quite clear. Are we jumping the gun when blaming antibiotics?

Fluoroquinolones are the most frequently implicated antibiotic class when it comes to concerns over dysglycemias. Oral and IV gatifloxacin was voluntarily removed from the market in 2006 after increasing public concern about a large series of reports of gatifloxacin-associated dysglycemias. However, as Aspinall *et al* propose, the incidence of reported adverse events may have been due to its relatively recent FDA approval in 1999. Research into the FDA’s voluntarily submitted adverse effects data has shown a phenomenon called the Weber effect—a surge in adverse event reports that occurs during the first years of a drug’s market approval but tapers off during subsequent years.

Studies of fluoroquinolone effects on blood glucose have all been retrospective studies, and while they included large populations of patients with varying comorbidities, they were unable to analyze the possible association between fluoroquinolone use and the severity of a patient’s infection. It is also unusual that fluoroquinolones appear to cause both hypo and hyperglycemia at similar rates. The proposed mechanism for fluoroquinolone-induced hypoglycemia involves blockade of ATP-sensitive potassium channels in pancreatic beta cells, while the mechanism for hyperglycemia remains even less clear.

Ultimately, what these studies did show was that there was a significantly larger proportion of patients taking gatifloxacin who were reported to be hospitalized for dysglycemia compared with the non-fluoroquinolone antibiotics. Levofloxacin was also associated with a small but significant increase in hospitalization, though ciprofloxacin was not. If this research is taken at face value, then dysglycemia does not appear to be a class effect for the fluoroquinolones.

Cautious use of antibiotics is still warranted, especially in patients who are prone to dysglycemias or renal insufficiency such as elderly and diabetic patients. However, clinicians should always consider the likelihood of dysglycemia occurring due to infection relative to the chance that it may have been caused by an antibiotic. Close attention should be paid to glucose levels whenever these high risk patients are ill, as the body’s adrenergic response to infection and changes in the patient’s behavior while ill will both affect glucose metabolism. Diabetic patients should be educated to carefully monitor their blood glucose during these times, and warned to take extra care if their eating habits have changed, for instance during a hospitalization.

## Fluoroquinolones

What are the dangers?



### References:

1. Aspinall SL, Good CB, Jiang R, McCarren M, Dong D, Cunningham FE. Severe Dysglycemia with the Fluoroquinolones: A Class Effect? *Clinical Infectious Diseases*. 2009;49:402-8. DOI: 10.1086/600294.
2. Park-Wyllie LY, Juurlink DN, Kopp A, Shah BR, Stukel TA, Stumpo C, Dresser L, Low DE, Mamdani MM. Outpatient Gatifloxacin Therapy and Dysglycemia in Older Adults. *N Engl J Med*. 2006;354:1352-61. DOI: 10.1056/NEJMoa055191.
3. Gurwitz JH. Serious Adverse Drug Effects—Seeing the Trees through the Forest. *N Engl J Med*. 2006;354:1413-15. DOI: 10.1056/NEJMe068051.

# Literature Review

## **Bromocriptine: What is Its Role in Diabetes?**

By: Christina Inteso, Pharm.D. Candidate 2014



*“Despite its high incidence of adverse events, bromocriptine QR deserves consideration as a treatment option for type 2 diabetic patients.”*

Bromocriptine-Quick Release (Cycloset<sup>®</sup>) was FDA approved in May 2009, as an adjunct to lifestyle modifications for the treatment of type 2 diabetes mellitus. Prior to this approval, bromocriptine (Parlodel<sup>®</sup>) was used for Parkinson's disease, macroprolactinemia, and acromegaly. For diabetes, bromocriptine QR is manufactured as 0.8 mg tablets and approved dosing is 0.8 mg to 4.8 mg per day. Bromocriptine QR should be started at 0.8 mg per day and titrated up weekly by one tablet until the maximum dose of 4.8 mg, intolerance, or desired A1C lowering is achieved. It should be taken within two hours of waking up and is recommended to be taken with food.<sup>1</sup>

Bromocriptine QR is a dopamine D<sub>2</sub> receptor agonist. Decreases in dopamine transmission from the hypothalamic-pituitary-adrenal (HPA) axis have been associated with insulin resistance, obesity, and increased triglyceride (TG) and free fatty acid (FFA) levels. Therefore, bromocriptine QR is thought to improve glucose tolerance, increase insulin sensitivity, reduce adiposity, and decrease TG and FFA levels. Research has also shown that diabetics tend to have lower dopamine levels in the morning, which explains why this medication should be given within two hours of waking up.<sup>2</sup>

There have been four randomized, placebo-controlled trials that have shown bromocriptine to be effective in lowering glycosylated hemoglobin (A1C), fasting blood glucose (FBG), and postprandial glucose levels in type 2 diabetics. As monotherapy, the trials have shown that bromocriptine QR will lower A1C by 0.4 to 0.9%, FBG by 23-31 mg/dL, and post-prandial glucose levels by 37 mg/dL. As add-on therapy, bromocriptine QR has decreased A1C by 0.5-0.6% from a baseline of 8.3% and has lowered FBG by 14 mg/dL. TG levels were also decreased by 29% and FFA levels fell by 19% from baseline. There were no statistically significant changes in LDL, HDL, or systolic blood pressures; and rates of hypoglycemia were similar between bromocriptine QR (6.9%) and placebo (5.3%).<sup>3</sup>

With regard to safety outcomes, bromocriptine QR was shown to demonstrate serious adverse event rates comparable to placebo during a one year randomized, double-blind, placebo-controlled trial. Among bromocriptine QR treated patients, 89% reported an event while 83% of patients reported an event in the placebo group. However, 24% of the bromocriptine QR treatment group discontinued the medication compared with only 11% in the placebo group. The most frequently reported adverse events were nausea, vomiting, dizziness, headache, fatigue, and diarrhea. These events were commonly seen during initiation and titration of the medication but usually diminished after 2 weeks of treatment. This same study also assessed cardiovascular outcomes among bromocriptine treated patients and found that serious adverse cardiovascular events occurred in 8.6% of the bromocriptine QR group and 9.6% of the placebo group. The composite cardiovascular outcome of myocardial infarction, stroke, coronary revascularization, or hospitalization for angina or heart failure was also studied and found to occur in 1.8% of the bromocriptine QR group compared with 3.2% of the placebo group, which correlated with a 40% risk reduction for cardiovascular disease in patients treated with bromocriptine.<sup>4</sup>

Based upon this clinical trial data, despite its high incidence of adverse events, bromocriptine QR deserves consideration as a treatment option for type 2 diabetic patients. Bromocriptine QR has demonstrated reasonable efficacy in reducing A1C levels as monotherapy as well as an add-on agent and also has beneficial effects on FBG, post-prandial glucose, TG, FFA, BP and is relatively weight neutral. Bromocriptine QR has positive cardiovascular outcomes and ultimately may be most beneficial in patients with CVD and CVD risk factors. Patients who have problems with frequent or severe hypoglycemia or weight gain may also derive significant benefit from this agent.

### Clinical Pearls:

- \* Cannot be interchanged with Parlodel<sup>®</sup>
- \* If dose is missed, skip that dose and resume the next morning
- \* Somnolence, hypotension, syncope risk during initiation and dose titration
- \* Drug interactions with antipsychotic drugs, medications metabolized by CYP 3A4, and protein bound drugs
- \* Avoid in women who are breastfeeding
- \* Cost of \$27.30 to \$163.80 per month through the VA depending on dosage

### References:

1. Cycloset [Package Insert]. Santarus, Inc.; 2010
2. Grunberger G. Novel therapies for the management of type 2 diabetes mellitus: Part 1. Pramlintide and bromocriptine-QR. *J Diabetes*. 2013;5(2):110-7.
3. Garber AJ, Blonde L, Bloomgarden ZT, et al. The Role of Bromocriptine-QR in the Management of Type 2 Diabetes Expert Panel Recommendations. *Endocr Pract*. 2013;19(1):100-6.
4. Gaziano JM, Cincotta AH, O'Connor CM, et al. Randomized Clinical Trial of Quick-Release Bromocriptine Among Patients With Type 2 Diabetes on Overall Safety and Cardiovascular Outcomes. *Diabetes Care*. 2010;33(7):1503-8.



# Clinical Specialist Corner



Dr. Heather Ulrich has been with the Lebanon VA Medical Center for 6 years as one of the facility's chief diabetes educators. Upon arriving in Lebanon, Heather took over the operation of the nurse practitioner run Diabetes Education Clinic, and the clinic has only grown from there. Today the Diabetes Education Clinic provides care for hundreds of Vet-

erans at Lebanon with the help of 3 full-time clinical pharmacists as well as a number of pharmacy residents and students.

Before coming to the VA Heather completed her PGY-1 residency training at Temple University Hospital before moving on to the Providence Medical Center in Portland, Oregon for her PGY-2 specialization in ambulatory care. Heather then went on to accept a position with the University of Colorado School of Pharmacy, where she split her time between teaching and practicing in the university hospital's ambulatory care clinics. Luckily for the diabetic Veterans in Lebanon, despite enjoying her time on the West Coast,

Heather eventually returned home to Central Pennsylvania to be closer to family and to accept her current position as a clinical pharmacist and diabetes educator.

Outside of work you can find Heather hiking, biking, snowboarding or doing pretty much anything to stay active and enjoy the outdoors. In her free time Heather also likes to travel and support the Philadelphia professional sports franchises. No matter how she spends her time though, you can be certain that Heather will always find a way to make the most of her experiences.



## VA National

## National Brand to Generic

### Formulary Changes

### Conversions 2014

#### Additions:

- Zonisamide  
*Restricted to Neurology*
- Oxcarbazepine  
*Restricted to Neurology*

#### Removals:

- Balsam Peru/Castor Oil/  
Trypsin

- |  |  |
|--|--|
| • Asacol <sup>®</sup> —January 2014    | • Nexium <sup>®</sup> —May 2014        |
| • Trillipix <sup>®</sup> —January 2014 | • Xeloda <sup>®</sup> —June 2014       |
| • Rapamune <sup>®</sup> —January 2014  | • Actonel <sup>®</sup> —June 2014      |
| • Avelox <sup>®</sup> —February 2014   | • Nasonex <sup>®</sup> —July 2014      |
| • Evista <sup>®</sup> —March 2014      | • Lumigan <sup>®</sup> —August 2014    |
| • Celebrex <sup>®</sup> —May 2014      | • Copaxone <sup>®</sup> —November 2014 |
| • Lunesta <sup>®</sup> —May 2014       |  |

# Patient Safety Alerts

## FDA to Review Heart Failure Risk with Saxagliptin

The FDA's decision to review saxagliptin was the result of a study published in the New England Journal of Medicine (NEJM), which reported an increased rate of hospitalization for heart failure with use of saxagliptin (marketed as Onglyza<sup>®</sup> and Kombiglyze XR<sup>®</sup>) compared to an inactive treatment. However, the study did not find increased rates of death or other major cardiovascular risks, including heart attack or stroke, in patients



who received saxagliptin. At this time, the FDA considers information from the NEJM study to be preliminary and

recommends that patients should not stop taking saxagliptin and should speak with their health care professionals about any questions or concerns. Health care professionals should continue to follow the prescribing recommendations in the drug labels. The FDA has also revealed that analysis of the saxagliptin clinical trial data is part of a broader evaluation of all type 2 diabetic drug therapies and cardiovascular risk.

## Clarification on Revatio<sup>®</sup> Use in Pediatric Patients

The FDA is clarifying its previous recommendation related to prescribing Revatio<sup>®</sup> (sildenafil) for children with pulmonary arterial hypertension. The FDA revised the Revatio<sup>®</sup> drug label in August 2012, adding a warning stating that "use of Revatio<sup>®</sup>, particularly chronic use, is not recommended in children." This recommendation was based on an observation of increased mortality with in-

creasing Revatio<sup>®</sup> doses in a long-term clinical trial in pediatric patients with pulmonary hypertension. However, the FDA would like to clarify the strength of this recommendation by noting that pediatric use is not an absolute contraindication to prescribing Revatio<sup>®</sup>. There may still be situations in which the risk-benefit profile of Revatio<sup>®</sup> would be acceptable

in individual children, for example, when other treatment options are limited and Revatio<sup>®</sup> can be used with close monitoring. It will be up to the discretion of the healthcare professional to assess risk versus benefit and determine, which patients would benefit most from the use of Revatio<sup>®</sup>.

**"Pediatric use is not an absolute contraindication to prescribing Revatio<sup>®</sup>."**

## Use of Doripenem to Treat Pneumonia in Ventilated Patients

The FDA has concluded that doripenem carries an increased risk of death and lower clinical cure rates compared to use of imipenem and cilastatin for injection. Based on an FDA analysis of data from a three-year clinical trial that was prematurely stopped in 2011 due to these safety concerns, the FDA

has approved changes to the doripenem drug label that describe these risks. In the clinical trial, patients with ventilator-associated bacterial pneumonia received either 7-day doripenem treatment or 10-day treatment with imipenem and cilastatin. In the intent-to-treat population, the 28-day all-cause mortality

was higher in the doripenem arm (23.0%; n=31/135) than in the imipenem and cilastatin arm (16.7%; n=22/132). Clinical cure rates were also lower in the doripenem arm. Doripenem is no longer approved to treat any type of pneumonia but is still considered safe and effective in the treatment of adults with complicated intra-abdominal infections and urinary tract infections.



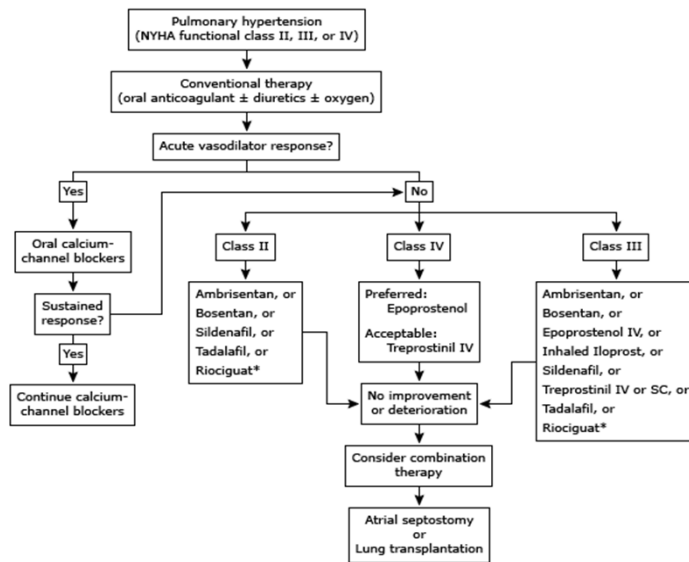
## New Drug Update

Continued from Page 1






Riociguat is specifically indicated for pulmonary arterial hypertension to increase exercise capacity, improve WHO functional class, and to delay clinical worsening of the disease (see algorithm below). It is supplied as a 1 mg tablet for oral administration. The recommended initial dose is 1 mg taken three times a day, titrated in increments of 0.5 mg to a maximum dose of 2.5 mg three times daily. Common adverse events associated with riociguat include but are not limited to: hypotension, headache, dizziness, nausea/vomiting, and diarrhea.

Approval for the use of riociguat in pulmonary hypertension is based on the PATENT-1 trial, a multi-center, double-blind, randomized, placebo-controlled trial of 445 subjects with pulmonary hypertension who were either treatment-naïve or being treated with an endothelin receptor antagonist or a prostacyclin analog. The subjects were randomized to receive either placebo or two different doses of

riociguat orally over a period of 12 weeks. The primary endpoint was change from baseline in the six-minute walking distance test after 12 weeks of treatment. Subjects treated with riociguat showed an improvement of 36 meters ( $p < 0.0001$ ) after 12 weeks compared with placebo. Trial results also showed a statistically significant improvement in both the treatment-naïve group (38 meters after 12 weeks compared with placebo) and the pre-treated group (36 meters after 12 weeks compared with placebo). Based upon these outcomes riociguat is now recommended for both WHO functional class II and III pulmonary hypertension.



## Can You Name That Drug?

- 1) 
- 2) 
- 3) 
- 4) 
- 5) 

Try to sound out the name of the drug based on the picture clues provided

- Answers:
- 1) Tacrolimus
  - 2) Prozac
  - 3) Maraviroc
  - 4) Dronedarone
  - 5) Lasix